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CLINICAL TRIAL REPORT

Phase I clinical trial of intrathecal gemcitabine in patients with neoplastic meningitis

Ronald J. Bernardi · Lisa Bomgaars · Elizabeth Fox · Frank M. Balis · Merrill J. Egorin · Theodore F. Lagattuta · Alberta Aikin · Patricia Whitcomb · Jamie Renbarger · Frank S. Lieberman · Stacey L. Berg · Susan M. Blaney

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Abstract
Purpose A phase I study of intrathecal (IT) gemcitabine was performed to define a safe dose and characterize the toxicity profile and CSF pharmacokinetics of gemcitabine and its major metabolite 2′,2′-difluoro-deoxyuridine (dFdU) in patients 3 years of age and older with neoplastic meningitis.
Experimental design Gemcitabine was administered via Ommaya reservoir or lumbar puncture at three dose levels: 5 mg weekly, 5 mg twice-weekly, and 10 mg twice-weekly using a standard phase I dose escalation design. Serial CSF samples were obtained for pharmacokinetic studies in seven patients with Ommaya reservoirs. Serial blood samples for pharmacokinetic studies were also obtained from three patients.
Results Ten patients were enrolled in this study. Significant neurological toxicities occurred in two patients including myelitis in a patient at the 5 mg twice-weekly dose level and somnolence in a patient at the 10 mg twice-weekly dose level. No complete responses were seen; however, three patients had stable disease. Gemcitabine was rapidly eliminated from the CSF with a terminal half-life of 61 ± 50 min. No gemcitabine or dFdU was detected in plasma.
Conclusions IT gemcitabine was associated with significant neurotoxicity; therefore, its further development for IT use is not recommended.

Keywords Intrathecal · Gemcitabine · Phase I · Pharmacokinetic

R. J. Bernardi · L. Bomgaars · J. Renbarger · S. L. Berg · S. M. Blaney
Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, USA

E. Fox · F. M. Balis · A. Aikin · P. Whitcomb
The Pediatric Oncology Branch, National Cancer Institute, NIH Bethesda, Bethesda, MD 20892, USA

M. J. Egorin · T. F. Lagattuta
Molecular Therapeutics/Drug Discovery Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15213, USA

M. J. Egorin · F. S. Lieberman
Departments of Medicine and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Present Address:
J. Renbarger
Riley Children's Hospital, Indianapolis, IN, USA

S. M. Blaney (✉)
Texas Children's Cancer Center, 6621 Fannin, MC 1410.00, Houston, TX 77030, USA
e-mail: sblaney@txccc.org

Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine or dFdC) is a deoxycytidine analogue that inhibits DNA polymerase and ribonucleotide reductase. It has pre-clinical and clinical activities against a wide variety of cancers including pancreatic [4, 16, 27], lung [24, 28], breast [25], bladder [12, 23], ovarian [18], testicular [3, 10], and head and neck cancers [6, 19], as well as leukemias and lymphomas [21]. However, as is the case for many other chemotherapeutic agents, the blood–cerebrospinal (CSF) barrier limits the CSF penetration of intravenously administered gemcitabine. In a nonhuman primate model, the area under the concentration versus time curve in CSF was only 7% of that in

plasma [15]. Thus, leptomeningeal tumor spread, an increasingly common occurrence with improvements in frontline therapy for many solid tumors, remains difficult to treat effectively or prevent with systemically administered chemotherapy [2, 13, 22]. Intrathecal (IT) administration of anticancer agents is one strategy that has the potential to circumvent the blood–CSF barrier; however, relatively few agents are currently available for IT administration, particularly agents with efficacy against solid tumors and primary CNS tumors that are metastatic to the leptomeninges [26].

In a nonhuman primate model that is predictive of the CNS pharmacology of anticancer drugs in humans [20] we demonstrated a substantial pharmacokinetic advantage for IT administration of gemcitabine. CSF gemcitabine concentrations after a 5 mg IT dose were more than 200-fold of plasma concentrations achieved with a standard intravenous dose [9]. Short-term administration of weekly intralumbar gemcitabine was well tolerated in this model. The feasibility of IT gemcitabine administration was anecdotally described in a 54-year-old male with leptomeningeal carcinomatosis from non-small cell lung cancer [7]. He received five weekly 200 mg doses of intraventricular gemcitabine following premedication with intraventricular dexamethasone (10 mg) but unexpectedly died of a myocardial infarction 3 days following the fifth dose. The results of our preclinical studies and this case report served as the bases for initiating a phase I clinical trial of IT gemcitabine in patients with neoplastic meningitis.

Materials and methods

Patient eligibility

Patients were eligible for this trial if they were ≥3 years of age and had neoplastic meningitis, secondary to an underlying leukemia, lymphoma or solid tumor that was refractory to conventional therapy. Patients with leukemia or lymphoma were required to have a CSF cell count >5 μL^{-1} and evidence of blasts on cytospin preparation or cytology. Patients with solid tumors were required to have the presence of tumor cells on cytospin preparation, cytology, or presence of leptomeningeal disease on MRI scans. Other eligibility criteria included (1) life expectancy of ≥6 weeks; (2) Karnofsky performance status of ≥50% for patients >10 years old or a Lansky performance status of ≥50% for patients ≤10 years old; (3) recovery from the acute neurotoxic effects of prior therapy and no uncontrolled systemic illness (e.g., infection); (4) no systemic CNS-directed therapy within 3 weeks, craniospinal irradiation within 8 weeks, or any IT therapy within 1 week prior to starting treatment on this study; (5) absolute neutrophil count > 1,000 μL^{-1}, platelet count > 40,000 μL^{-1}, and hematocrit > 30%; (6) total bilirubin < 2.0 mg/dL and SGPT < 5 times the upper limit of normal; and (7) serum creatinine < 2 times the upper limit of normal for age. Patients were not eligible if they were receiving investigational agents, chemotherapeutic agents that significantly penetrate the CSF [e.g. high-dose methotrexate (>1 g/m^2), thiotepa, high-dose cytarabine (>1 g/m^2), 5-fluorouracil, intravenous 6-mercaptopurine, nitrosoureas, temozolomide, or topotecan], or drugs known to have serious, unpredictable CNS side effects. Other exclusion criteria included (1) clinical evidence of obstructive hydrocephalus; (2) compartmentalization of CSF flow on a radioisotope CSF flow study; (3) clinically significant serum electrolyte abnormalities including calcium, magnesium, and phosphorus; (4) a ventriculoperitoneal or ventriculoatrial shunt; (5) leukemia or lymphoma with a concomitant bone marrow relapse; (6) pregnancy or lactation; and (7) the potential for impending spinal cord compression.

Informed consent was obtained from all patients or their legal guardians (if the patient was <18 years of age) in accordance with institutional guidelines, and patients <18 years of age were involved in all discussions in order to obtain verbal assent as appropriate.

Dosage and drug administration

Gemcitabine (hydrochloride salt) was supplied by Eli Lilly as a lyophilized powder in 200 mg vials. The powder was dissolved in 5 mL of preservative-free 0.9% sodium chloride and then further diluted in the appropriate amount of preservative-free, pyrogen-free 0.9% sodium chloride to a final volume of 10 mL. Drug was administered using a 25-gauge needle at a rate of 2 mL/min via lumbar puncture or via Ommaya reservoir. Drug administration was isovolumetric, i.e. an equivalent volume of CSF was removed prior to administration of drug. Following administration of the drug to patients with an Ommaya reservoir, the reservoir was flushed for 1–2 min with approximately 2 mL of preservative-free, 0.9% sodium chloride and then pumped 4–6 times. All patients were hospitalized overnight for the first dose of gemcitabine and were observed for a minimum of 2 h after subsequent doses.

The initial dose level was 5 mg weekly for 6 weeks during induction. Subsequent cohorts received IT gemcitabine twice-weekly at doses of 5 and 10 mg for 6 weeks. At the completion of 6 weeks of induction, patients who did not have disease progression or DLT were eligible to proceed to consolidation, which was given weekly for 6 weeks at the same dose as induction and beginning 1 week after the final dose of induction. Patients who completed consolidation and who did not have disease progression or DLT proceeded to maintenance, which included twice-monthly IT gemcitabine for 4 months and monthly thereafter for a total

duration of therapy of 1 year at the dose level (5 or 10 mg) they received for induction.

Patients who experienced arachnoiditis could receive dexamethasone 0.15 mg/kg bid po or iv for 3–5 days and immediately prior to subsequent doses of IT gemcitabine. If arachnoiditis recurred in subsequent courses despite prophylactic dexamethasone, then the dose of IT gemcitabine was reduced to the previous dose level for subsequent doses.

Three patients were entered at each dose level, and there was no intrapatient dose escalation. Dose escalation proceeded to the next level after the three patients at the previous level completed four doses, later amended to 4 weeks, of induction therapy without experiencing a DLT. If one of the first three patients at a dose level experienced a DLT, up to three additional patients were added at that dose level. When DLT was observed in two patients of a cohort, the maximum tolerated dose (MTD) was exceeded, and three more patients were treated at the next lower dose level, assuming <6 had previously been treated at that dose level.

Pretreatment and follow-up studies

A complete history and physical examination including a detailed neurological examination were obtained prior to treatment, weekly, during induction and consolidation; twice-monthly for 4 months during maintenance and then monthly thereafter. CSF was evaluated for WBC and differential count, protein, glucose, and cytospin or cytology for malignant cells, immediately prior to the first dose of gemcitabine, 24 h after the first dose, weekly during induction, every 2 weeks during consolidation, and monthly during maintenance. In patients with Ommaya reservoirs, lumbar CSF was evaluated at the completion of induction and consolidation and every 3 months during maintenance.

Laboratory evaluation included a complete blood count with differential and platelets, BUN, serum creatinine, SGPT, electrolytes, calcium, magnesium, phosphorus, and total bilirubin weekly during induction and consolidation and monthly during maintenance. Patients with solid tumor had an indium^{111}-DTPA or technetium^{99}-DTPA CSF flow study prior to entry, and patients with leukemia/lymphoma had a pre-treatment radionuclide CSF flow study if CSF analysis or MRI scan suggested CSF blockage. Patients with solid tumor and patients with leukemia or lymphoma with a positive MRI at diagnosis had an MRI of the head and spine with and without contrast prior to consolidation and maintenance and every 3 months during maintenance.

Criteria for assessment of toxicity and response

Toxicities were evaluated using Version 2.0 of the NCI Common Toxicity Criteria. Dose-limiting toxicity was defined as any grade 3 or higher neurotoxicity or other organ toxicity considered to be primarily related to IT gemcitabine. Exceptions to this were grade 3 toxicities such as headache or emesis that could be well controlled with supportive and preventative measures during subsequent doses.

A CR was defined as complete clearing of malignant cells from CSF by cytology and complete clearance of the evidence of disease on MRI on two consecutive MRI scans. PD was defined as an increase of >25% in the size of measurable lesions on MRI or new sites of leptomeningeal enhancement or an increase in the CSF cell count and the presence of blasts when compared to the lowest CSF cell count with defined cutoffs based on the initial CSF cell count. Stable disease was defined as failing to fulfill the criteria for either a CR or PD.

Pharmacokinetic studies

CSF for pharmacokinetic studies was collected in tubes containing 0.05 mg tetrahydrouridine (Calbiochem, La Jolla, CA, USA) in order to prevent ex-vivo deamination of gemcitabine. Ventricular CSF samples (0.5 mL) were obtained prior to drug administration and at 5, 15, 30, 45, and 60 min and 2, 3, 6–8, and 24 h following drug administration. CSF samples were centrifuged at 1,000*g* for 10 min. The supernatant was transferred to a polypropylene tube and stored at −70°C until analysis. In three patients, 5 mL blood samples were collected in heparinized tubes containing 0.5 mg tetrahydrouridine. Blood was sampled at the same times as for CSF. Blood samples were centrifuged at 1,000*g* for 10 min, and the resulting plasma was transferred to a polypropylene tube and stored at −70°C until analysis.

Concentrations of gemcitabine and dFdU in CSF and plasma were determined by HPLC using a previously published and validated method [29].

Pharmacokinetic parameters were estimated by noncompartmental methods. The area under the drug concentration versus time curve (AUC) was derived by the linear trapezoidal method [11]. Total CSF clearance (CL_{CSF}) was determined by dividing the dose by the CSF AUC.

Results

Ten patients enrolled in the study. Patient characteristics are shown in Table 1. All patients were eligible, and all were evaluable for toxicity.

Toxicity

The toxicities attributed to IT gemcitabine administration are shown in Table 2. As described in detail below, there were two patients with dose-limiting neurological adverse events: one of six patients treated at the 5 mg twice-weekly

Table 1 Patient characteristics ($n = 10$)

Male/female	5/5
Age (years)	
Median	25
Range	8–59
Prior treatment regimens	
Median	3
Range	1–7
Diagnoses	
ALL[a]	4
Breast cancer	3
Non-small cell lung cancer	1
Medulloblastoma	1
Synovial cell sarcoma	1

[a] *ALL* acute lymphoblastic leukemia

Table 2 Adverse events attributed to IT gemcitabine

Toxicity	Gemcitabine dose level		
	5 mg weekly ($n = 3$)	5 mg twice weekly ($n = 6$)	10 mg twice weekly ($n = 1$)
Nausea/vomiting			
Grade 1	1	1	
Grade 2	1		
Thrombocytopenia			
Grade 1		1	
Fatigue			
Grade 1		1	
Drooling			
Grade 1		1	
Stiff neck			
Grade 1		1	
Arachnoiditis			
Grade 1		1	
Grade 2		1	
Myelitis			
Grade 3		1	
Headache			
Grade 2		1	
Altered mental status			
Grade 2		1	
Aphasia			
Grade 2		2	
Somnolence			
Grade 3			1
Seizures			
Grade 2			1
Tremors			
Grade 1			1

dose level developed transverse myelitis, and the first patient treated at the 10 mg twice-weekly dose level developed somnolence. According to the initial protocol, accrual would have continued to determine whether there was a second DLT at the 10 mg twice-weekly dose level. However, we felt that the two DLTs observed were of sufficient severity to halt further development of this agent. The Data Safety Monitoring Committee for the protocol concurred with this decision.

The DLT at the 5 mg twice-weekly dose level occurred in a 9-year-old boy with his seventh CNS relapse of acute lymphoblastic leukemia. The patient had non-dose-limiting headache and fever consistent with arachnoiditis after his second dose of IT gemcitabine. He was treated with dexamethasone per protocol and had resolution of his symptoms. The patient received concurrent oral dexamethasone with subsequent IT gemcitabine doses without recurrence of the arachnoiditis. After his tenth dose of intraventricular gemcitabine, the patient developed urinary retention, which required intermittent catheterization, and fecal incontinence. An MRI of the brain revealed new ependymal enhancement at the site of his Ommaya catheter, consistent with focal ventriculitis. An MRI of the spine showed a large patchy area of increased signal on T2 from the dens to the top of C4 (Fig. 1), as well as enhancement of the posterior columns from the level of the cervico-medullary junction to the level of the C3–C4 interspace. The thoracic cord showed enhancement consistent with transverse myelitis or leukemic infiltration. Diffuse leptomeningeal enhancement of the distal cord, conus, and cauda consistent with arachnoiditis was also noted. The CSF–WBC was 1 μL^{-1}, and there were no leukemic blasts on cytospin. Therefore, the urinary retention, fecal incontinence, and radiographic

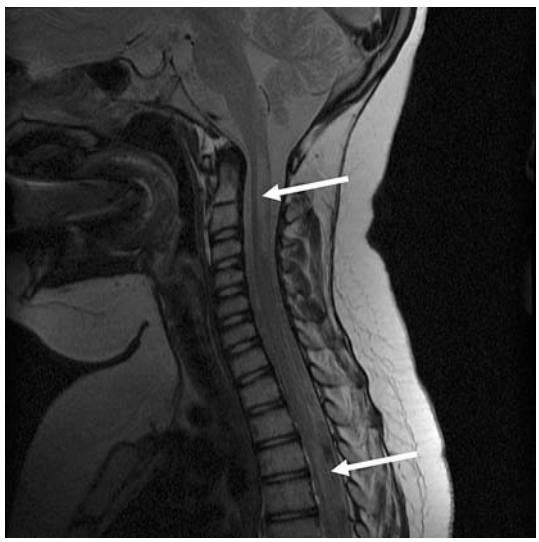

Fig. 1 Sagital T2-weighted image showing the increased signal from the dens to the top of C4 and increased signal as well as changes in the thoracic cord

findings were felt to be most consistent with transverse myelitis. These signs and symptoms resolved over the ensuing 6 months while the patient was receiving liposomal cytarabine (DepoCyt); however, his CNS leukemia subsequently recurred.

The second patient with dose-limiting neurological toxicity was a 43-year-old woman who was treated with the 10 mg twice-weekly dose level for meningeal breast cancer. She developed grade 3 somnolence after her seventh dose of intraventricular gemcitabine. She also experienced mild tremors that began 1 h after her third dose of gemcitabine. Prior to her fourth dose of gemcitabine she experienced grade 2 seizures when her Ommaya reservoir was pumped. The dose of gemcitabine was not given and the therapy with levetiracetam was initiated. The patient experienced another seizure at home and was admitted to the hospital. Phenytoin was added as an anti-seizure medication when the patient experienced another seizure with a subsequent Ommaya reservoir tap. An MRI showed that the Ommaya reservoir tip was in place and that the underlying leptomeningeal disease appeared to be stable. Following a comprehensive neurological re-evaluation, the seizures were attributed to the underlying neoplastic meningitis, particularly because, additional history revealed that they had commenced prior to the treatment with gemcitabine. The fifth and sixth doses of gemcitabine were well tolerated. However, after the seventh dose the patient had intermittent periods of depressed consciousness that progressed to overt somnolence over the ensuing 24 h. She was removed from the study for presumed disease progression. However, over the next several days her neurological status returned to baseline at which point the somnolence was attributed to the gemcitabine.

Response

Five patients completed induction therapy. There were no objective responses. Three patients had stable disease, and one of them completed 9 weeks of maintenance. Three patients did not complete induction therapy due to disease progression. Two had clinical progression after four and nine doses, respectively. One died of clinical disease progression after the seventh dose. As noted above, neurological toxicity prevented two patients from completing induction therapy.

Pharmacokinetics

CSF pharmacokinetic data were available for seven patients enrolled at the 5 mg dose level. The pharmacokinetic parameters for gemcitabine and its deaminated metabolite, difluorodeoxyuridine (dFdU), are shown in Table 3. The elimination of gemcitabine was rapid with a median terminal half-life of 50 min. There was minimal conversion of gemcitabine to its inactive metabolite, dFdU. The median dFdU CSF AUC was <1.1% (range 0.3–1.7%) of the parent drug CSF AUC. Neither gemcitabine nor dFdU were detected in plasma samples.

Discussion

Metastatic spread to the leptomeninges portends a poor prognosis, in part, because of limited treatment options. IT chemotherapy preventively administered has lowered the incidence of meningeal relapse and improved the outcome for patients with leukemias and lymphomas, but there are very few IT agents with activity against refractory meningeal leukemias or solid tumors. Gemcitabine has significant anti-tumor activity in a variety of tumor types that have a propensity to spread to the leptomeninges, and it exhibited a substantial pharmacokinetic advantage when given IT as compared to intravenously in nonhuman primates [9]. Therefore, we initiated a phase I trial of IT gemcitabine in patients with neoplastic meningitis.

Table 3 Gemcitabine pharmacokinetic data after a 5 mg intraventricular dose

Patient	Gemcitabine				dFdU		
	AUC_{tlast} (μg h/mL)	CL (mL/min)	$t_{½}\beta$ [a] (min)	C_{max} [b] (μg)	AUC_{tlast} (μg h/mL)	$t_{½}\beta$ [a] (min)	C_{max} [b] (μg)
1	583	0.14	72	283	9.97	246	1.25
3	157	0.39	28	248	0.5	168	0.32
4	378	0.19	168	186	12.4	270	0.67
5	533	0.16	20	458	6.2	120	1.61
6	327	0.25	56	192	6	72	1.76
7	210	0.38	35	184	2.6	96	0.69
8	197	0.42	49	181	3.4	132	0.89
Mean	341	0.28	61	247	5.7	158	1.03
SD	168	0.12	50	101	4.2	75	0.53

[a] terminal half-life

[b] maximum CSF concentration

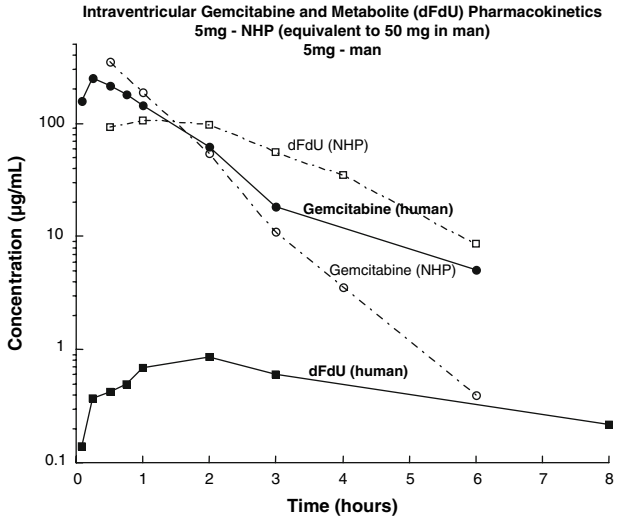

Fig. 2 *Concentration* versus *time* curves of 5 mg dose of intraventricular gemcitabine (dFdc) and dFdU in man and nonhuman primates. Nonhuman primate dose is equivalent to 50 mg in man. *Points* geometric mean from three data sets in man (one) and nonhuman primates (two). Nonhuman primate data in the figure is from studies performed by Egorin MJ et al. [9]

Table 4 Ratio of dFdU to gemcitabine (U:C) in plasma and CSF for cytidine analogues

Cytidine analogue	U:C plasma		U:C CSF	
	Monkey	Human	Monkey	Human
Gemcitabine	145[b]	25[c]	1.2[d]	0.017
Cytarabine	30[e]	10[f]	0.43[h]	0.049[g]
CPE-C[a]	4[e]	0.6[h]	–	–
2′,3′-dideoxycyticine	0.1[i]	U.D[j]	–	–

[a] *CPE-C* cyclopentenyl cytosine
[b] data from Ref. [15]
[c] data from Ref. [8]
[d] data from Ref. [9]
[e] data from Ref. [1]
[f] data from Ref. [8]
[g] data from Ref. [30]
[h] Blaney et al. unpublished data
[i] data from Ref. [14]
[j] data from Ref. [17]

The preclinical studies on which this phase I trial was based were performed in a nonhuman primate model that was previously used to predict the CSF pharmacokinetics of IT anti-cancer drugs in humans. Unlike humans, there was substantial conversion of gemcitabine to dFdU in the animals (Figs. 1, 2). The mean ratio of the uridine to cytidine moieties in nonhuman primates was 1.2 [9], compared to 0.017 in humans due to a difference in cytidine deaminase levels [1, 5]. Nonhuman primates deaminate cytidine and its analogues such as cytarabine and gemcitabine, more efficiently in plasma and CSF (Table 4). The starting dose in humans on this trial was approximately one tenth of the equivalent dose (adjusted for the ten-fold difference in CSF volume) evaluated in nonhuman primates. The lower dose in humans produced an area under the concentration versus time curve equivalent to that of the primates. Although, this AUC was not associated with clinical evidence of toxicity in the chronic dosing studies performed in nonhuman primates [9], dose-limiting neurological toxicity was observed in patients who had received prior central-nervous system directed therapy including IT chemotherapy and radiation therapy. Based on the clinical experience, we conclude that the potential for severe neurotoxicity precludes further development of gemcitabine for IT administration.

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